
Effectiveness of Neuraminidase Inhibitors for Preventing Staff Absenteeism during Pandemic Influenza

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We used a deterministic SEIR (susceptible-exposed-infectious-removed) meta-population model, together with scenario, sensitivity, and simulation analyses, to determine stockpiling strategies for neuraminidase inhibitors that would minimize absenteeism among healthcare workers. A pandemic with a basic reproductive number (R_0) of 2.5 resulted in peak absenteeism of 10%. Treatment decreased peak absenteeism to 8%, while 8 weeks' prophylaxis reduced it to 2%. For pandemics with higher R_0 , peak absenteeism exceeded 20% occasionally and 6 weeks' prophylaxis reduced peak absenteeism by 75%. Insufficient duration of prophylaxis increased peak absenteeism compared with treatment only. Earlier pandemic detection and initiation of prophylaxis may render shorter prophylaxis durations ineffective. Eight weeks' prophylaxis substantially reduced peak absenteeism under a broad range of assumptions for severe pandemics (peak absenteeism >10%). Small investments in treatment and prophylaxis, if adequate and timely, can reduce absenteeism among essential staff.

Concerns regarding the advent and impact of the next influenza pandemic have led >120 countries to develop pandemic preparedness plans (1). Studies have shown that treatment with neuraminidase inhibitors and prophylaxis of selected subpopulations are cost-effective strategies to limit the pandemic's impact on the healthcare system (2,3). However, supplies of neuraminidase inhibitors are limited, and countries may not have the financial resources to purchase large stockpiles. Policymakers will thus have to determine priorities for treatment and prophylaxis.

One priority is to maintain essential services during the pandemic's peak—to ensure business continuity and mitigate the resultant damage. Absenteeism of essential staff from work should be minimized to prevent service disruption when most needed. This is particularly crucial for healthcare workers (HCWs) because they may have an increased risk for exposure and illness while facing a surge in demand for healthcare services.

A recent study proposed that hospitals should consider stockpiling neuraminidase inhibitors for treatment and prophylaxis (4). To provide policy guidance to reduce the pandemic's impact on HCWs, this study analyzed the use of neuraminidase inhibitors in minimizing absenteeism by simulating an HCW population in a transmission dynamics model.

Methods

Model Structure and Dynamics

We used a deterministic, modified SEIR (susceptible-exposed-infectious-removed) meta-population model to evaluate strategies for minimizing absenteeism among HCWs during an influenza pandemic. The model consisted of 2 distinct populations in Singapore: the general population and an HCW population (Figure 1A). Singapore's mid-year population in 2005 was 4.35 million, and the public HCW population of 20,000 represented essential staff that required protection. Oseltamivir was the neuraminidase-inhibitor modeled because of its effectiveness in treatment and prophylaxis, good safety profile, and common use in national stockpiles (5–8). Standard treatment regimen was 75 mg, twice per day for 5 days, and prophylaxis required 75 mg once per day for as long as planned.

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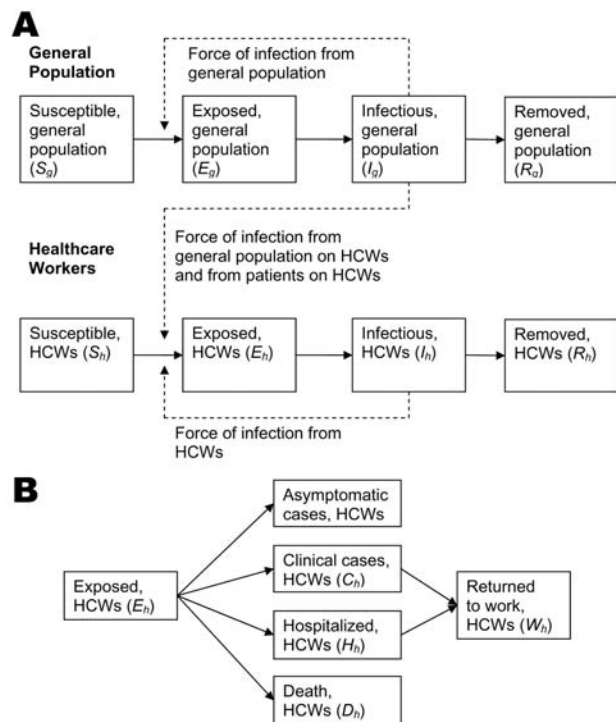


Figure 1. A) Modified SEIR (susceptible-exposed-infectious-removed) model for transmission of pandemic influenza within the general population and healthcare worker (HCW) subpopulation. B) Absenteeism among exposed HCWs.

This study assumed that the general population did not receive treatment or prophylaxis with oseltamivir. Three strategies for HCWs were considered: no action (providing symptomatic relief), treatment only (early treatment of all symptomatic HCW infections), and prophylaxis (prophylaxis together with early treatment). Different predetermined prophylaxis substrategies were considered, based on the weeks of prophylaxis; each additional week required 140,000 doses in addition to separate treatment stockpiles. To be conservative, we assumed that prophylaxis stockpiles would last only for the planned duration. Separate analyses explored the effect of stopping prophylaxis after individual clinical infection, with redistribution of prophylaxis doses to other HCWs to prolong prophylaxis beyond the planned duration; however, this strategy is only possible if tests can promptly confirm individual infection and logistics networks allow for redistribution.

We assumed that all persons were susceptible to the pandemic virus and that the general population epidemic occurred as a single wave after introduction of a single infectious case. We ignored the contribution of new introductions after the start of the epidemic. Persons were removed from the susceptible state, after infection, through recovery or death (Figure 1A). Births, deaths from

other causes, immigration, and emigration during the period were assumed to be negligible.

We assumed a range of infectious periods similar to those from other studies; we also assumed that the disease was infectious at about the same time a person became symptomatic; i.e., the latent period coincided with the incubation period (9,10). A range of basic reproductive numbers (R_0), based on these infectious and latent periods, were then used to generate epidemics in the general population with varying rates of transmission. These R_0 then determined the course of the HCW epidemic.

HCWs were assumed to be exposed to influenza from 3 sources and may be more likely to be exposed than the general population (11). The first source was exposures from colleagues (HCW-to-HCW transmission) at a proportion (ω); the second was from persons outside the workplace ($1-\omega$). In the absence of published estimates, the base case assumed that 50% of infections were attributed to HCW-to-HCW transmission, with sensitivity analysis performed from 20% to 80%. The third source was from general population case-patients (patient-to-HCW transmission), expressed as the ratio of susceptible HCWs who could be infected by incident case-patients who sought treatment from the healthcare system (H/P). The extent of transmission is dependent on interventions such as barrier precautions (11). On the basis of findings from exploratory analysis, increasing the H/P ratio moves the HCW epidemic earlier; at an H/P of 2.08, the HCW epidemic peaks before the start of prophylaxis, negating the outcomes of prophylaxis. Therefore, H/P values >2 do not substantially contribute to the outcomes and study conclusions, and sensitivity analysis was performed for H/P from 0 to 2 (online Technical Appendix, available at www.cdc.gov/EID/content/13/3/449_app.htm). Transmission from HCWs to patients was assumed negligible compared with other sources of infection for the general population, and the general population epidemic was independent of transmission dynamics within the HCW population.

Once infected, an HCW would have 4 outcomes based on absenteeism (Figure 1B). Those with asymptomatic infection were assumed to be fit for work. Absenteeism due to symptomatic infection, hospitalization, and death was determined for the different strategies. The study assumed that all HCWs were absent from work while symptomatic and that prophylaxis reduced HCW-to-HCW transmission (9). Each scenario was further analyzed on the basis of different R_0 , the disease's incubation and infectious periods were kept constant.

Pandemic Duration and Prophylaxis Initiation

The point of local detection of pandemic influenza depends on various factors and is unknown. Approximately 2,800 cases of influenzalike illness (ILI)

occur per day in Singapore (2), of which a small fraction is sampled for virologic surveillance (12). The base case assumed that the pandemic influenza subtype would be detected when incident symptomatic cases exceeded 10% of baseline ILI rates. The pandemic duration was defined as the period when incident pandemic influenza cases remained above this stated level. Prophylaxis was given to HCWs at the time of disease detection and continued for the planned duration. We conducted sensitivity analysis for starting prophylaxis on introduction of the first case and when incident cases exceeded 1%–100% of the baseline ILI rate.

Other Input Parameters

The input parameters for analysis (Table 1) were obtained from local sources when available as detailed in

a previous study on stockpiling strategies in Singapore (2). Other values were obtained from international sources. To account for uncertainties, wide ranges were used for analysis.

HCWs were assumed to be adults 20–64 years of age with a mix of persons at low and high risk for influenza complications similar to that in the general population. Hospitalization and case-fatality rates were estimated for a pandemic of average severity (2). To account for the effect of severe pandemics, a scenario using death rates from the 1918 “Spanish flu” (5% average) and correlated hospitalization rates was performed (19).

Outcome Variables and Sensitivity Analysis

Outcome variables from the analyses included pandemic duration, peak staff absenteeism, and days with

Table 1. Parameters of neuraminidase inhibitor stockpiling strategies model*

Parameter	Notation†	Minimum‡	Base case‡	Maximum‡	Reference
Input					
General population	N_g		4,350,000		(13)
Healthcare staff	N_h		20,000		Estimated
ILI rate, per day	ι		2,800		(2)
Transmission dynamics					
Incubation and latent period, d	α	1.0	2.0	3.0	(9,10)
Infectious period, d	γ	1.5	4.1	7.0	(9,10)
Reproductive number	R_0	1.5	2.5	6.0	(9,14)
Transmission probability/d	β	0.37	0.61	2.0	Calculated, R/γ
HCW-to-HCW transmission	ω	0.2	0.5	0.8	See text
HCW infections caused by incident cases of clinical influenza (H/P)	δ	0		2.0	See text
Detection threshold, proportion of baseline ILI rate	ν	Introduction of 1st case	0.1	1	See text
Disease severity and antiviral efficacy					
Hospitalization rate (HCW)/100,000 infected§	η	12.4	88.6	186.7	(2)
Length of stay and medical leave if hospitalized, d	ϕ	9.0	12.0	20.0	(2)
Case-fatality rate (HCW)/100,000 infected§	μ	1.9	20.3	65.1	(2)
Proportion of infected persons without prophylaxis who have symptoms	θ_1	0.50	0.67	0.80	(9,15)
Oseltamivir efficacy for preventing infection in exposed persons	ε_1	0.28	0.35	0.52	(9,16,17)
Oseltamivir efficacy for preventing disease in infected persons	ε_2	0.5	0.6	0.9	(2,9)
Oseltamivir efficacy for preventing transmission of infection by infected persons	ε_3	0.6	0.8	0.98	(9)
Proportion of infected persons receiving oseltamivir prophylaxis who have symptoms	θ_2	0.07	-	0.2	Calculated, $\theta_2 = \theta_1(1-\varepsilon_2)$
Medical leave without treatment, d	σ	2	4	5	(2)
Reduction in medical leave with oseltamivir treatment, d	χ	0.1	1.0	2.0	(2)
Reduction in hospitalization or case-fatality rate with treatment	ψ	0.4	0.6	0.8	(2,18)

*HCW, healthcare workers; ILI, influenzalike illness.

†Notations are used in the equations listed in the Appendix.

‡Base case values are given with the minimum and maximum values used in the model where applicable.

§Based on hospitalizations and deaths among those with clinical influenza.

absenteeism >5%. For parameters relating to disease severity and antiviral efficacy, 1-way sensitivity analysis was performed to determine the effect on outcomes. In addition, Monte Carlo simulation analysis, with 1,000 iterations per scenario, was performed with the range of parameter estimates modeled as triangular distributions. For parameters pertaining to transmission dynamics, separate analyses were performed to determine the effects of variations in HCW-to-HCW and patient-to-HCW transmission. We also tested the outcome effects of assuming different latent and infectious periods. Epidemics with similar R_0 but different latent and infectious periods have different growth rates. To facilitate comparison between epidemics with different latent and infectious periods, both epidemic growth rates and R_0 values were presented. The relationship between latent and infectious period, R_0 , and growth rates was described by Mills et al. (14) and elaborated in the Online Technical Appendix. Finally, the outcomes were determined for the various strategies upon initiation of prophylaxis at different times.

We used Berkeley-Madonna 8.3 software (University of California, Berkeley, CA, USA) to run the model. Details of the equations are shown in the Appendix; additional methods and results are shown in the Online Technical Appendix.

Results

The epidemic curve for a base-case pandemic with R_0 of 2.5 had a 12-week duration (Figure 2). When no action was taken, peak HCW absenteeism was $\approx 10\%$. Treatment only, using 121,000 doses of oseltamivir, decreased peak absenteeism to 8%. Prophylaxis for 4 weeks required 117,000 treatment doses in addition to 560,000 dedicated prophylaxis doses (equivalent to treatment courses for 1.6% of the general population) and led to higher peak absenteeism than treatment only. Eight weeks of prophylaxis required 52,000 treatment doses in addition to 1.12 million dedicated prophylaxis doses (equivalent to treatment courses for 2.7% of the general population) and reduced peak absenteeism to $\approx 2\%$; the peak occurred as a secondary increase after termination of prophylaxis. Discontinuing prophylaxis for clinical infections and redistributing stockpiles to prolong prophylaxis in other HCWs did not provide additional outcome benefits because the doses saved were insignificant; >96% were used during the preplanned duration for the relevant scenarios. From the Monte Carlo simulation of peak absenteeism for different strategies in a pandemic with R_0 of 2.5, with varying disease severity and antiviral efficacy parameters, 6 weeks of prophylaxis was sufficient under all scenarios to have a net benefit over treatment only (Figure 3).

One-way sensitivity analyses showed that the following input parameters had the most effect on peak absen-

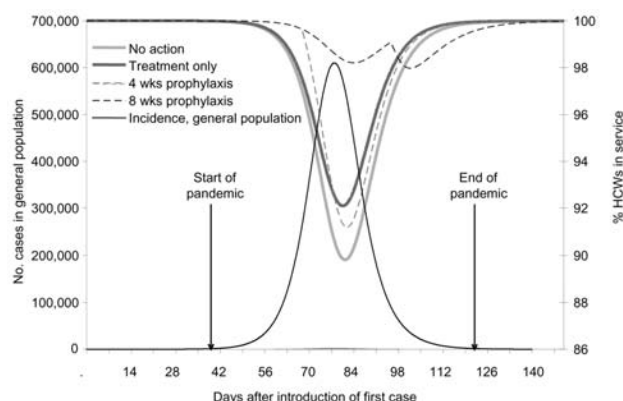


Figure 2. Dynamics of population infections and the effect of different strategies on absenteeism among healthcare workers for a base-case pandemic.

teeism: “days of medical leave without treatment,” with 15%–96% variation from the baseline outcome, depending on the R_0 and strategy used; “reduction in medical leave with treatment” with 22%–61% variation; “symptomatic proportion in infected persons without prophylaxis” with 19%–25% variation; and “oseltamivir efficacy in preventing disease in infected persons” with 21%–87% variation. Other input parameters had less effect on the outcome.

Table 2 shows the outcomes for pandemics with different R_0 . If no action was taken for pandemics with $R_0 \geq 2$, absenteeism exceeded 5% for >15 days. In pandemics with lower R_0 (≤ 2), pandemic durations were longer and peak absenteeism did not exceed 10%. Treatment only in these pandemics reduced peak absenteeism by as much as 25% compared with no action. However, prophylaxis of ≈ 8 weeks did not accrue substantial benefits over treatment only.

Pandemics with higher R_0 (≥ 4) were of shorter durations; peak absenteeism was >20% in some scenarios. Treatment only reduced peak absenteeism by >15%, and 6 weeks of prophylaxis was sufficient to reduce peak absenteeism by >75% over no action. Across all R_0 , insufficient durations of prophylaxis increased peak absenteeism compared with results for treatment only.

During a pandemic similar in severity to the 1918 influenza pandemic, with a 5% mortality rate and R_0 of 4 (14), peak absenteeism reached 20% with no action; hospitalizations and deaths contributed substantially to absenteeism, unlike the situation in less severe pandemics. The 3 strategies—treatment only, 4 weeks of prophylaxis, and 6 weeks of prophylaxis—reduced peak absenteeism by 25%, 43%, and 80%, respectively.

We also tested the adequacy of prophylaxis for a base-case pandemic under different scenarios for HCW-to-HCW and patient-to-HCW transmission. Higher HCW-to-HCW transmission resulted in an increased postprophylaxis epi-

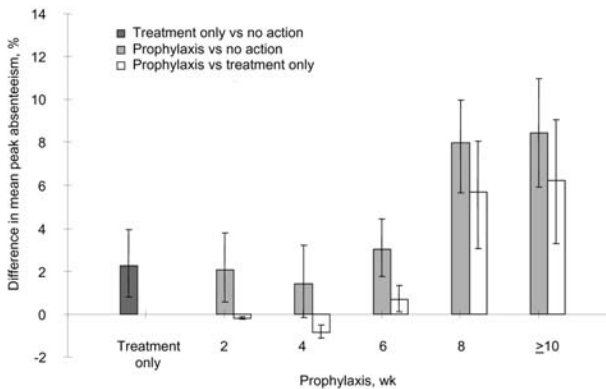


Figure 3. Simulation analysis of the difference in mean peak absenteeism for different strategies in an $R_0 = 2.5$ (base-case) pandemic (50th percentile shown in solid bars with the 5th and 95th percentiles shown in error bars).

demic peak. The HCW epidemic coincided with the general population epidemic if the patient-to-HCW infections variable was minimized ($H/P = 0$). Increasing H/P alone shifted the HCW epidemic such that it preceded the general population epidemic and amplified peak absenteeism by as much as 1.4× for the base case. For the prophylaxis strategies, increasing the patient-to-HCW transmission resulted in the distribution of HCW absenteeism away from the postprophylaxis period into the pre- and intraprophylaxis periods, which resulted in lower peak absenteeism up to a point. For $H/P > 2.0$, peak absenteeism occurred before initiation of prophylaxis, negating the effect of longer durations of prophylaxis. Under all HCW-to-HCW and patient-to-HCW transmission scenarios for a base-case pandemic, 6 weeks of prophylaxis provided equal or superior results to treatment only; 8 weeks of prophylaxis was always superior (Online Technical Appendix).

Figure 4 shows the changes in peak absenteeism when latent and infectious periods were varied. For any rate of growth, assuming different latent periods changed peak absenteeism by <1% for most scenarios; assuming longer infectious periods increased peak absenteeism by <3%.

However, epidemics with higher growth rates for any latent and infectious periods increased peak absenteeism by >10% when no action was taken. Although changes in the transmission parameters substantially changed peak absenteeism levels for certain scenarios, the overall conclusions remained similar. For epidemics with low peak absenteeism (<10%) and prolonged duration (low growth rate), prophylaxis strategies were less effective than treatment only. In contrast, for epidemics with higher peak absenteeism (>10%) and shorter duration (high growth rate), prophylaxis of ≥6 weeks was superior to treatment only.

Figure 5 shows the adequacy of prophylaxis for a base-case pandemic under different prophylaxis initiation points based on pandemic detection. Earlier detection and prophylaxis initiation resulted in a greater likelihood that shorter durations of prophylaxis would be ineffective. If prophylaxis were initiated on entry of the first pandemic case, 14 weeks of prophylaxis would be required for maximal benefit. Prophylaxis for 6 weeks was more effective than treatment only if it was initiated when incident pandemic cases in the general population exceeded 10% of the ILI rate, whereas 8 weeks of prophylaxis was effective when incident pandemic cases exceeded 1%.

Discussion

During an influenza pandemic, essential services such as healthcare must be maintained, especially during the pandemic's peak, when the maximal number of patients require care, and healthcare services can ill afford absenteeism due to infection. Absenteeism may also occur for reasons such as background illnesses and the need to care for ill relatives. During the severe acute respiratory syndrome epidemic in Singapore in 2003, schools were closed for weeks. Although no study documented the resultant workplace absenteeism, parents may have taken time off to care for their children. The New Zealand government has predicted overall absenteeism levels as high as 40% (20), and actual pandemic workplace absenteeism levels will likely exceed those shown in this study.

Table 2. Effects of influenza pandemic prevention strategies on healthcare worker absenteeism

Reproductive no. (R_0)	Pandemic duration, wk	Peak % absent by strategy (days with >5% absent)					
		No action	Treatment only	2 weeks' prophylaxis	4 weeks' prophylaxis	6 weeks' prophylaxis	8 weeks' prophylaxis
1.5	24	2.8 (0)	2.1 (0)	2.1 (0)	2.1 (0)	2.2 (0)	2.3 (0)
2	15	6.7 (17.8)	5.1 (5.4)	5.2 (6.5)	5.5 (9.1)	5.9 (11)	4.6 (0)
2.5	12	10.2 (21.1)	7.9 (16)	8.1 (16.2)	8.8 (16.2)	7.2 (10.8)	2 (0)
3	10	13 (20.6)	10.2 (16.6)	10.6 (16.7)	11.4 (15)	4.7 (0)	2.5 (0)
4	8	17.3 (18.7)	13.9 (15.7)	14.6 (15.4)	10.8 (11.1)	3.7 (0)	3.7 (0)
6	6	22.5 (16.5)	18.5 (13.9)	19.7 (12.9)	5.5 (4.1)	5.5 (4.1)	5.5 (4.1)
Pandemic similar to 1918 "Spanish flu"		20.2 (28.6)	15.1 (18.3)	15.8 (17.9)	11.6 (13)	4.1 (0)	4.1 (0)

* $R_0 = 4$; mortality rate = 5% (hospitalization set to the ratio of the hospitalization rates to the case-fatality rates in Table 1).

Treatment and timely use of prophylaxis with neuraminidase inhibitors reduce HCW absenteeism compared with no action. As shown in previous studies, treatment provides benefits over no action and should be considered

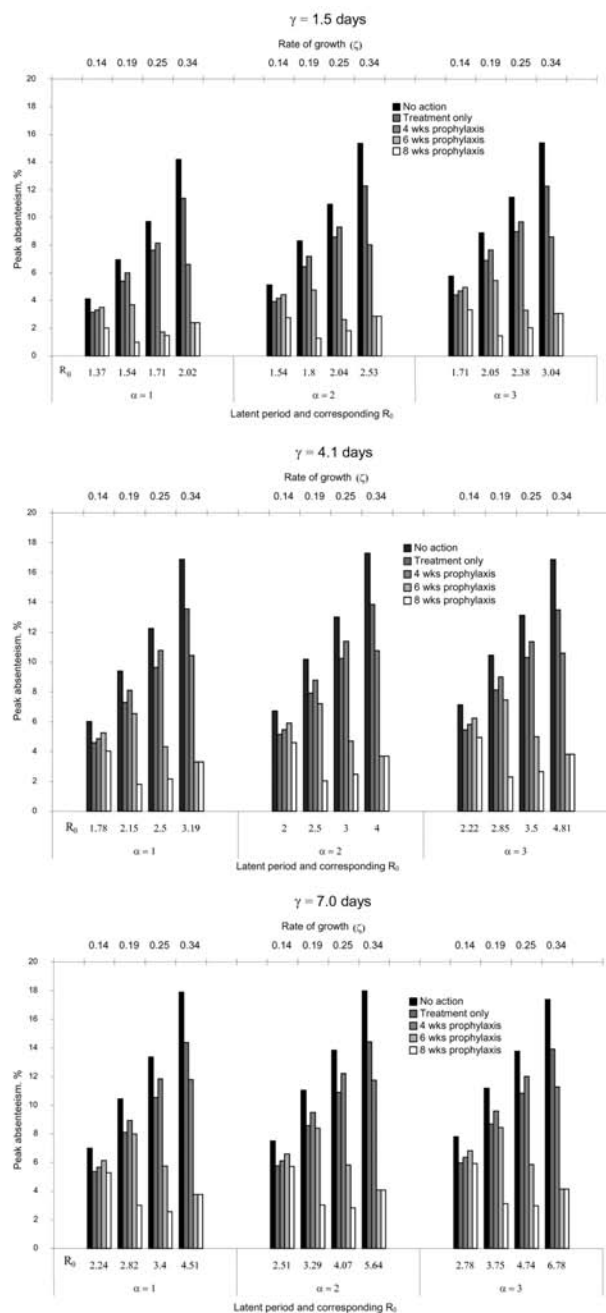


Figure 4. Peak absenteeism with different treatment (Tx) and prophylaxis (Rx) strategies varying rates of growth (ζ)*, latent periods (α), and infectious duration (γ). * ζ is the initial rate of growth of the epidemic curve and is determined by the reproductive potential and the infectious agent's doubling time (T). The latter is related to the rate of growth by the following equation:

$$T = \frac{\ln(2)}{\zeta}$$

in preparedness plans to reduce illness and death (2,3,21). Using prophylaxis to prevent infection results in a secondary increase in infections after prophylaxis is stopped because HCWs remain susceptible at a time when transmission in the general population is ongoing. Insufficient durations of prophylaxis thus result in poorer outcomes than treatment only. For prophylaxis strategies to accrue more benefits than treatment only, the prophylaxis duration must be sufficient to cover the pandemic's peak. Eight weeks of prophylaxis, the maximum safe duration previously studied (22), was sufficient to provide a substantial reduction in peak absenteeism under a broad range of assumptions for more severe pandemics where peak absenteeism exceeded 10%. Six weeks of prophylaxis was marginally beneficial, if one assumes that prophylaxis was initiated after incident pandemic cases exceeded 10% of the baseline ILI rate.

An important policy consideration is the timing of prophylaxis initiation. Improved surveillance, critical for early detection, paradoxically increases the likelihood of initiating prophylaxis too early, causing predetermined stockpile durations to be inadequate. Many countries have developed comprehensive preparedness plans to reduce a pandemic's spread. These may prolong the pandemic's duration within the country, which would compound the issue of stockpile adequacy. If prophylaxis is started prematurely, stockpiles will be exhausted before the delayed waves of the pandemic occur and thus will not reduce absenteeism more than would treatment only. Prophylaxis should not be initiated until a certain point in the epidemic curve, but this may be difficult, given public sentiment and pressure. Further studies are needed to determine the ideal time for prophylaxis initiation and the role of surveillance in evaluating the pandemic phases and projected spread.

The current avian influenza outbreaks have increased fear of an imminent severe pandemic. Pandemics of lesser severity place fewer requirements on essential services. Our study showed that such pandemics also result in lower staff absenteeism rates; treatment and prophylaxis may thus be less critical to service continuity. On the contrary, severe pandemics increase the strain because of the numbers of patients, hospitalizations, and deaths and the reduced response capacity of healthcare services. For pandemics with high mortality rates, high growth rates, or high R_0 , prophylaxis provides greater benefits than it does for pandemics with lower mortality rates, low growth rates, or low R_0 ; and the required duration of prophylaxis is shorter.

Our results are subject to several limitations. The true level of transmission in HCWs remains unknown. In a heightened state of alertness, HCWs will be equipped with personal protective equipment, and patient-HCW transmission may be minimized, resulting in lower absenteeism rates (10). Another limitation is that effects over the entire

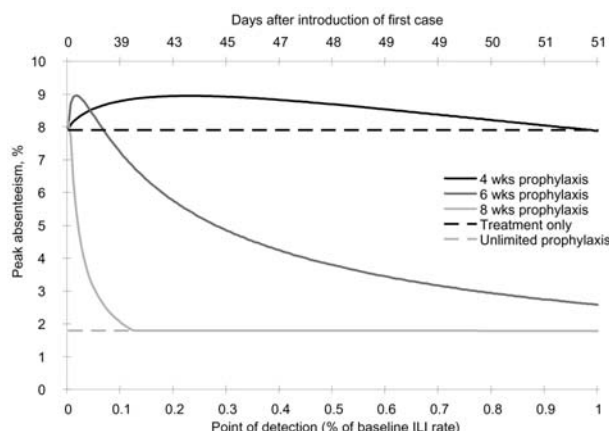


Figure 5. Peak absenteeism observed with different times of initiating prophylaxis, according to point of detection in a base-case pandemic. ILI, influenzalike illness.

HCW population were aggregated. In reality, subsets of HCWs exist with varying levels of exposure. Stochastic variation and nosocomial outbreaks, which were not modeled, may result in higher local absenteeism rates than predicted by this model. Further studies that use individual-based stochastic models may provide improved representation of disease transmission to test other interventions. Studies should also consider modeling the effect of multiple pandemic waves. Finally, the study parameters used were based on historical data; the validity of the projections will depend on how the next pandemic compares with its precedents.

Conclusion

Countries must consider the effects of an influenza pandemic on essential services. Those planning neuraminidase inhibitor stockpiling for treatment and prophylaxis of essential staff should consider the relatively small quantities required. Treatment and 8 weeks of prophylaxis for HCWs in Singapore costs US \$2 million, compared with US \$400 million for a similar populationwide stockpile and the ≈US \$20 million spent for national stockpiling (2). In severe pandemics, when the need for protection is greatest, prophylaxis of short duration has a potential role in mitigating the effects. For prophylaxis strategies to succeed, stockpiles must be adequate and their deployment must be timed to cover the pandemic's peak. If adequacy and timeliness cannot be achieved, prophylaxis may result in higher absenteeism than treatment only, which makes the latter strategy a more effective option.

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Appendix

Modified SEIR Model

The model was run across 365 days at time steps of 0.05 days. The equations used in the analysis are shown below; the notations are represented in Table 1.

General Population

For the general population, persons move from the susceptible (S_g) to the exposed (E_g), infected (I_g), and removed (R_g) states as shown in the respective equations below.

$$\frac{d(S_g)}{dt} = -\beta \frac{I_g}{N_g} S_g$$

$$\frac{d(E_g)}{dt} = \beta \frac{I_g}{N_g} S_g - \frac{E_g}{\alpha}$$

$$\frac{d(I_g)}{dt} = \frac{E_g}{\alpha} - \frac{I_g}{\gamma}$$

$$\frac{d(R_g)}{dt} = \frac{I_g}{\gamma}$$

Where β is the transmission probability per day from an average infectious person, N_g is the size of the general population, α is the incubation period, and γ is the infectious period.

HCW Population

Transmission and disease severity parameters are determined by whether HCWs are given treatment and/or prophylaxis. The use of treatment and prophylaxis is indicated by the variables i and j , respectively. $i = 0$ denotes when treatment is not in use, and $j = 0$ when prophylaxis is not in use, and $i = 1$ and $j = 1$ denote when treatment and prophylaxis are in use, respectively. The use of prophylaxis is conditional to the pandemic having been detected and the stockpile, P , not having been exhausted.

Transmission Dynamics

For the HCW population, persons move through the susceptible (S_h), exposed (E_h), infected (I_h), and removed (R_h), states as shown below:

$$\frac{d(S_h)}{dt} = -(\lambda_h + \lambda_g + \lambda_p)(1 - j\varepsilon_1)S_h$$

$$\frac{d(E_h)}{dt} = (\lambda_h + \lambda_g + \lambda_p)(1 - j\varepsilon_1)S_h - \frac{E_h}{\alpha}$$

$$\frac{d(I_h)}{dt} = \frac{E_h}{\alpha} - \frac{I_h}{\gamma}$$

$$\frac{d(R_h)}{dt} = \frac{I_h}{\gamma}$$

where N_h is the size of the HCW population. j indicates the use of prophylaxis, so that when $j = 1$, HCWs have a reduced susceptibility to infection due to the efficacy of prophylaxis in preventing infection (ε_1), and are the forces of infection acting on HCWs.

λ_h is the force of infection from HCW-to-HCW transmission within the workplace, and is defined as the following:

$$\lambda_h = \omega\beta(1 - j\varepsilon_2)\frac{I_h}{N_h}$$

where ω is the proportional contribution due to HCW-to-HCW transmission to the force of infection, and ε_2 is the efficacy of oseltamivir in reducing infectiousness, which renders a proportion of HCWs on prophylaxis noninfectious when $j = 1$.

λ_g is the force of infection from exposure of HCWs to the general population during the proportion of their time spent outside the workplace. The force of infection is similar to that in the general community, subject to the proportion of time spent outside the workplace ($1 - \omega$). λ_g is thus defined as

$$\lambda_g = (1 - \omega)\beta\frac{I_g}{N_g}$$

λ_p is the additional force of infection from patient-to-HCW transmission due to symptomatic incident patients as they enter the healthcare system with pandemic influenza (occupational hazard). No discrimination between the probability of acquiring infection in the community healthcare or hospital healthcare setting is represented, because the actual probability of transmission in either setting is unknown. Influenza patients are assumed to be distributed randomly among the HCW population and to have an aggregated probability δ of infecting susceptible HCWs with whom they come into contact, regardless of single or multiple contact episodes or duration of contact. The rate at which new symptomatic infections from the general population will present to the healthcare system at any point in time would be

$$\frac{\theta_1 E_g}{\alpha}$$

Therefore, the force of infection for each HCW, λ_p is as follows:

$$\lambda_p = \frac{\delta\theta_1 E_g}{\alpha N_h}$$

where N_h is the number of HCWs under consideration.

We assumed that the small population of infectious HCWs did not affect the transmission dynamics of the disease in the general population.

Absenteeism

HCWs who are exposed will progress from the exposed state (E_h) to the states of asymptomatic infection, clinical infection (C_h), hospitalization (H_h), or death from the disease (D_h). Only the last 3 states contribute to absenteeism according to the respective durations off work as follows:

$$\frac{d(C_h)}{dt} = \theta_{j+1}(1 - (1 - i\psi)\eta) \frac{E_h}{\alpha} - \frac{C_h}{(\sigma - i\chi)}$$

$$\frac{d(H_h)}{dt} = \theta_{j+1}(1 - i\psi)(\eta - \mu) \frac{E_h}{\alpha} - \frac{H_h}{\phi}$$

$$\frac{d(D_h)}{dt} = \theta_{j+1}(1 - i\psi)\mu \frac{E_h}{\alpha}$$

where η is the hospitalized proportion, σ is the duration of medical leave in uncomplicated illness, ϕ is the duration of hospitalization and subsequent medical leave in complicated illness, and μ is the case-fatality proportion. ψ is the reduction in hospitalization or deaths with treatment, and χ is the reduction in medical leave with uncomplicated illness with treatment; both these terms are hence only active for values of $i = 1$. θ_{j+1} is the symptomatic proportion and hence takes the value of θ_1 in the absence of prophylaxis and θ_2 when prophylaxis is used, reflecting the efficacy of prophylaxis in reducing symptomatic disease (ϵ_2).

The number of healthcare staff in operation at any time is hence given as

$$O_h = N_h - C_h - H_h - D_h$$

The proportion absent at any given time is

$$\frac{O_h}{N_h}$$

We ignored the contribution of new recruitments after the start of the epidemic.

Incidence Rates, Start of Pandemic, and Use and Consumption of Prophylaxis Stockpile

The incident number of symptomatic cases of pandemic influenza in the general population, V_g , is given as

$$V_g = \frac{\theta_1 E_g}{\alpha}$$

The pandemic is deemed to start when

$$V_g > \nu t$$

where t is the baseline ILI rate, and ν is the detection threshold. When $V_g > \nu t$, then the predetermined stockpile, P , which is expressed as the number of days of prophylaxis stockpiled per HCW, begins to be consumed in strategies that use prophylaxis, i.e.,

$$\frac{d(P)}{dt} = -1$$

In a prophylaxis strategy, $j = 1$ when both conditions, $V_g > \nu t$ and $P > 0$, are satisfied; otherwise, $j = 0$.

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Appendix

Modified SEIR Model

The model was run across 365 days at time steps of 0.05 days. The equations used in the analysis are shown below; the notations are represented in [Table 1](#).

General Population

For the general population, persons move from the susceptible (S_g) to the exposed (E_g), infected (I_g), and removed (R_g) states as shown in the respective equations below.

$$\frac{d(S_g)}{dt} = -\beta \frac{I_g}{N_g} S_g$$

$$\frac{d(E_g)}{dt} = \beta \frac{I_g}{N_g} S_g - \frac{E_g}{\alpha}$$

$$\frac{d(I_g)}{dt} = \frac{E_g}{\alpha} - \frac{I_g}{\gamma}$$

$$\frac{d(R_g)}{dt} = \frac{I_g}{\gamma}$$

Where b is the transmission probability per day from an average infectious person, N_g is the size of the general population, a is the incubation period, and γ is the infectious period.

HCW Population

Transmission and disease severity parameters are determined by whether HCWs are given treatment and/or prophylaxis. The use of treatment and prophylaxis is indicated by the variables i and j , respectively. $i = 0$ denotes when treatment is not in use, and $j = 0$ when prophylaxis is not in use, and $i = 1$ and $j = 1$ denote when treatment and prophylaxis are in use, respectively. The use of prophylaxis is conditional to the pandemic having been detected and the stockpile, P , not having been exhausted.

Transmission Dynamics

For the HCW population, persons move through the susceptible (S_h), exposed (E_h), infected (I_h), and removed (R_h), states as shown below:

$$\frac{d(S_h)}{dt} = -(\lambda_h + \lambda_e + \lambda_p)(1 - jE_1)S_h$$

$$\frac{d(E_h)}{dt} = (\lambda_h + \lambda_e + \lambda_p)(1 - jE_1)S_h - \frac{E_h}{\alpha}$$

$$\frac{d(I_h)}{dt} = \frac{E_h}{\alpha} - \frac{I_h}{\gamma}$$

$$\frac{d(R_h)}{dt} = \frac{I_h}{\gamma}$$

where N_h is the size of the HCW population. j indicates the use of prophylaxis, so that when $j = 1$, HCWs have a reduced susceptibility to infection due to the efficacy of prophylaxis in preventing infection (ϵ_1), λ_g , λ_h and λ_p are the forces of infection acting on HCWs.

λ_h is the force of infection from HCW-to-HCW transmission within the workplace, and is defined as the following:

$$\lambda_h = \omega \beta (1 - j \epsilon_2) \frac{I_h}{N_h}$$

where ω is the proportional contribution due to HCW-to-HCW transmission to the force of infection, and ϵ_2 is the efficacy of oseltamivir in reducing infectiousness, which renders a proportion of HCWs on prophylaxis noninfectious when $j = 1$.

λ_g is the force of infection from exposure of HCWs to the general population during the proportion of their time spent outside the workplace. The force of infection is similar to that in the general community, subject to the proportion of time spent outside the workplace ($1 - \omega$). λ_g is thus defined as

$$\lambda_g = (1 - \omega) \beta \frac{I_g}{N_g}$$

λ_p is the additional force of infection from patient-to-HCW transmission due to symptomatic incident patients as they enter the healthcare system with pandemic influenza (occupational hazard). No discrimination between the probability of acquiring infection in the community healthcare or hospital healthcare setting is represented, because the actual probability of transmission in either setting is unknown. Influenza patients are assumed to be distributed randomly among the HCW population and to have an aggregated probability δ of infecting susceptible HCWs with whom they come into contact, regardless of single or multiple contact episodes or duration of contact. The rate at which new symptomatic infections from

the general population will present to the healthcare system at any point in time would be $\frac{\delta_1 E_g}{\alpha}$. Therefore, the force of infection for each HCW, λ_p is as follows:

$$\lambda_p = \frac{\delta \delta_1 E_g}{\alpha N_h} \text{ where } N_h \text{ is the number of HCWs under consideration.}$$

We assumed that the small population of infectious HCWs did not affect the transmission dynamics of the disease in the general population.

Absenteeism

HCWs who are exposed will progress from the exposed state (E_h) to the states of asymptomatic infection, clinical infection (C_h), hospitalization (H_h), or death from the disease (D_h). Only the last 3 states contribute to absenteeism according to the respective durations off work as follows:

$$\frac{d(C_h)}{dt} = \theta_{j+1}(1 - (1 - i\psi)\eta) \frac{E_h}{\alpha} - \frac{C_h}{(\sigma - i\chi)}$$

$$\frac{d(H_h)}{dt} = \theta_{j+1}(1 - i\psi)(\eta - \mu) \frac{E_h}{\alpha} - \frac{H_h}{\phi}$$

$$\frac{d(D_h)}{dt} = \theta_{j+1}(1 - i\psi)\mu \frac{E_h}{\alpha}$$

where η is the hospitalized proportion, σ is the duration of medical leave in uncomplicated illness, f is the duration of hospitalization and subsequent medical leave in complicated illness, and m is the case-fatality proportion. y is the reduction in hospitalization or deaths with treatment, and c is the reduction in medical leave with uncomplicated illness with treatment; both these terms are hence only active for values of $i = 1$. q_{j+1} is the symptomatic proportion and hence takes the value of q_1 in the absence of prophylaxis and θ_2 when prophylaxis is used, reflecting the efficacy of prophylaxis in reducing symptomatic disease (e_2).

The number of healthcare staff in operation at any time is hence given as

$$O_h = N_h - C_h - H_h - D_h$$

$$\frac{O_h}{N_h}$$

The proportion absent at any given time is

We ignored the contribution of new recruitments after the start of the epidemic.

Incidence Rates, Start of Pandemic, and Use and Consumption of Prophylaxis Stockpile

The incident number of symptomatic cases of pandemic influenza in the general population, V_g , is given as

$$V_g = \frac{\theta_1 E_g}{\alpha}$$

The pandemic is deemed to start when

$$V_g > \omega$$

where \bar{I} is the baseline ILI rate, and \bar{U} is the detection threshold. When $V_I > \bar{U}$, then the predetermined stockpile, P , which is expressed as the number of days of prophylaxis stockpiled per HCW, begins to be consumed in strategies that use prophylaxis, i.e.,

$$\frac{d(P)}{dt} = -1$$

In a prophylaxis strategy, $j=1$ when both conditions, $V_I > \bar{U}$ and $P > 0$, are satisfied; otherwise, $j=0$.

Technical Appendix

Supplementary material including additional methodology, results, and discussion.

Additional Methods

Treatment and prophylaxis stockpiles

Under the treatment only strategy, we considered the possibility that the treatment stockpiles may be limited. We analyzed the effect of varying the percentage of infected receiving treatment, on the outcome of peak absenteeism; for different R_0 . Under the prophylaxis strategies, we assumed that treatment stockpiles would be large enough to ensure sufficient treatment doses are available above those planned for use as prophylaxis.

We also explored the scenario that although the prophylaxis stockpiles are fixed at a certain quantity, a proportion of HCWs may develop clinical illness either before the start of, or during, prophylaxis. If these clinically infected HCWs can be identified as pandemic influenza infections, they would not need to continue receiving prophylaxis. The result is that some prophylaxis doses may be saved; and these saved doses may potentially be redistributed to the other non-clinically infected HCWs, prolonging prophylaxis beyond the planned duration. For example, if we originally stockpiled for 6 weeks of prophylaxis, and some HCWs could stop prophylaxis because they were clinically infected prior to the start of or during prophylaxis, then some doses could be saved and redistributed to other HCWs. This prolongs the duration of prophylaxis beyond the original 6 weeks. We have performed analyses to explore this scenario, although this is only possible if tests can promptly confirm individual infection and logistics networks allow for prompt redistribution. To address this issue from another angle, we explored the number of prophylaxis doses used at the end of the planned duration of prophylaxis for the various scenarios (based on R_0) if those who are clinically infected can be identified and prophylaxis stopped.

The total amount of oseltamivir used was also analyzed under the assumption that all HCWs consumed prophylaxis for the pre-planned duration, and ignoring the effect of the handful of deaths during prophylaxis and the few doses that may be saved when clinically infected HCWs on prophylaxis receive treatment doses drawn from the treatment stockpile.

Transmission dynamics

Transmission dynamics plays an important role in determining the growth of the epidemic and the shape of the epidemic curve, which in turn determines the overall epidemic duration and peak absenteeism. Similar to another modeling study, we assumed onset of symptoms coincided with the onset of infectiousness i.e. that the incubation period coincided with the latent period (1). The actual difference in timing and duration is probably less than a day for influenza since symptoms start on the same day as detectable viral shedding (2), and we hence assumed the same value (and corresponding symbol) to describe the incubation and latent periods in our study.

For our base case, we assumed a latent/incubation period of 2 days and an infectious period of 4.1 days, similar to base case values used by Mills et al in estimating R_0 from the 1918 pandemic (3). We then generated a set of epidemics with a range of growth rates by changing R_0 based on the above latent and infectious periods.

Outcome variables and sensitivity analysis

At lower R_0 of 2 or less, the impact of mis-timed prophylaxis is less of an issue, since the overall and peak absenteeism is low. At higher R_0 of more than 4, the epidemic progresses so quickly (about 6 weeks duration) that prophylaxis stockpiles will be sufficient to achieve their intended effect. The key scenarios of concern are those with R_0 between 2.5 to 4, as mis-timed prophylaxis can substantially exacerbate the effects of the outcomes. Under these scenarios, 4 to 8 weeks of prophylaxis can either be substantially more or less effective in reducing peak absenteeism compared to treatment only. Most of our sensitivity analyses were hence focussed on these combinations of scenarios.

Outcome variables from the analyses included pandemic duration, peak staff absenteeism, and days with absenteeism above 5%. We have focused our attention on peak staff absenteeism in the sensitivity analyses as a marker for comparison of the pandemic's impact on business continuity, as this will influence other outcomes. The number of days with absenteeism above 5% varies with peak absenteeism and pandemic duration (depending on the R_0), and does not provide for independent comparison across scenarios.

For parameters relating to disease severity and antiviral efficacy (previously studied parameters), one-way sensitivity analysis was performed to determine the impact on the outcomes. We performed separate one-way sensitivity analysis with different combinations of R_0 and management strategies (no action, treatment only, and prophylaxis). This is because each combination of R_0 and management strategy affects the outcomes on varying the input parameters. Certain input parameters such as efficacy of prophylaxis and effectiveness of treatment are not applicable to the strategies of treatment and no action, and were therefore excluded during analyses for the respective strategies. To facilitate interpretation on the effect of prophylaxis, we present results for sustained prophylaxis for the entire pandemic duration. Hospitalization and case fatality rates were scaled together based on their distributions, with the upper and lower limits fixed for both variables in a distribution centered on the mean. This is because hospitalization and case fatality rates are likely correlated during a pandemic (4).

In addition, Monte Carlo simulation analyses, with 1,000 iterations per scenario, were performed with the range of disease severity and antiviral efficacy parameter estimates modeled as triangular distributions. The result for the base case scenario has been shown in Figure 3 of the main manuscript, and we present the median, 5th, and 95th percentiles based on the various R_0 and strategies.

Parameters pertaining to transmission dynamics were analyzed separately because these values are future predictions whose distributions cannot be predicted by existing studies.

Sensitivity analyses based on multiple scenarios were also performed to determine if variation in HCW-to-HCW and patient-to-HCW transmission affected the outcomes. We explored one-way sensitivity analyses on these parameters for the outcomes of peak absenteeism; and the timing of peak absenteeism from introduction of the first case in the general population. We then explored the combined effect of varying both patient-to-HCW and HCW-to-HCW transmission parameters simultaneously in two-way sensitivity analyses.

To address the concern about how the different combinations of latent and infectious periods may affect the results, we conducted sensitivity analysis in which different latent and infectious periods were used. However, the growth rate of an epidemic is determined both by the reproductive potential as well as its generation time of the infectious agent (i.e. the time it takes to produce the successive generation of cases); for example, an epidemic caused by an infectious agent with an R_0 of 2 but a generation time of 3 days would grow at the same rate as an epidemic with an R_0 of 4 but a generation time of 6 days. To account for this, we defined a set of epidemics based on their growth rates, ζ , corresponding to $R_0 = 2.0$ to 4.0 with a latent period, α , of 2 days and an infectious period, γ , of 4.1 days. We then recalculated the corresponding R_0 for different parameter choices of α and γ based on the equation given by Mills et al (3). The equation is reproduced below, using our chosen notation for growth rates, and latent and infectious periods:

$$R_0 = 1 + \zeta(\alpha + \gamma) + \alpha\gamma\zeta^2$$

We modelled a broad range for latent and infectious periods, from $\alpha = 1$ to $\alpha = 3$ and from $\gamma = 1.5$ to $\gamma = 7$ (Table 1 of the main manuscript).

Additional Results

Figure A1 explores the sufficiency of treatment stockpiles for different R_0 . The outcomes of varying the percentage of infected individuals receiving treatment (due to limited stockpiles) lie progressively between the outcomes under no action and full treatment of all infected HCWs.

Table A1 compares peak absenteeism for HCW prophylaxis with re-distribution and without re-distribution (fixed pre-planned duration) of the prophylaxis doses. Redistribution of prophylaxis doses had none or only a marginal effect (in a few scenarios) on reducing peak absenteeism.

Table A2 shows the number of prophylaxis doses used at the end of the planned duration of prophylaxis for the various scenarios (based on R_0). For lower R_0 (≤ 2.5) or shorter pre-determined durations of prophylaxis (≤ 4 weeks), more than 90% of prophylaxis stocks were utilised by the end of the pre-determined duration of prophylaxis. For higher R_0 (≥ 3) or longer pre-determined durations of prophylaxis (> 8 weeks), less stocks were used but re-distribution of prophylaxis did not reduce peak absenteeism (Table A1) since pre-planned durations would already have been adequate. For the important scenarios (scenarios where an incremental increase in prophylaxis duration resulted in a sharp decrease in peak absenteeism as shown in Table A1), prophylaxis doses utilized remained above 93%.

Table A3 shows the treatment and prophylaxis doses required under the various strategies for the base case scenario ($R_0 = 2.5$). Prophylaxis doses constitute the overwhelming majority of the doses required for prophylaxis strategies of 4 weeks and above. The number of treatment doses required decreased for longer durations of prophylaxis, but the number of treatment doses saved under the different prophylaxis strategies is relatively negligible considering the number of prophylaxis doses required.

Disease severity and anti-viral efficacy parameters

For the following results, the scenarios with values of R_0 from 2.5 to 4.0, and the most viable strategies of 4 to 8 weeks of prophylaxis should be focused on, because of their substantial impact on the outcome.

Figures A2 to A4 show the results of one-way sensitivity analyses with different combinations of R_0 and management strategies. Regardless of the values of R_0 , for a given strategy, the outcomes are most sensitive to the same parameters.

For the strategy of no action, "days of medical leave without treatment" and "symptomatic proportion in infected persons without prophylaxis" had a substantial effect on the outcomes. "Days of medical leave without treatment" had 15% to 49% variation from the baseline outcome depending on the R_0 ; while "symptomatic proportion in infected persons without prophylaxis" had 19% to 25% variation. The outcomes were insensitive to hospitalization, case-fatality and the length of hospitalization in symptomatic infections.

The treatment only strategies were sensitive to the "reduction in medical leave with oseltamivir treatment", in addition to "days of medical leave without treatment" and "symptomatic proportion in infected persons without prophylaxis". "Days of medical leave without treatment" had 20% to 96% variation from the baseline outcome depending on the R_0 ; "reduction in medical leave with treatment" had 22% to 60% variation; and "symptomatic proportion in infected persons without prophylaxis" had 19% to 25% variation. The outcomes were insensitive to the other input parameters.

Prophylaxis strategies were also sensitive to the efficacy of anti-virals when used as prophylaxis, such as "oseltamivir efficacy in preventing infection in exposed persons", "oseltamivir efficacy in preventing disease in infected persons", "oseltamivir efficacy in preventing transmission of infection by infected persons"; in addition to the factors for treatment only. "Oseltamivir efficacy in preventing disease in infected persons" had 21% to 87% variation from the baseline outcome depending on the R_0 ; "oseltamivir efficacy in preventing infection in exposed persons" had 5% to 25% variation; "oseltamivir efficacy in preventing transmission of infection by infected persons" had 5% to 8% variation; "days of medical leave without treatment" had 25% to 75% variation; "reduction in medical leave with treatment" had 23% to 61% variation; and "symptomatic proportion in infected persons without prophylaxis" had 19% to 25% variation. The outcomes were insensitive to the other input parameters.

Table A4 gives the multi-way sensitivity analysis using Monte-Carlo simulation (1,000 iterations) for disease severity and anti-viral efficacy parameters. For $R_0 \geq 2.5$, 8

weeks of prophylaxis provided results that were sufficiently close to providing prophylaxis throughout the entire pandemic. For lower R_0 (≤ 2), prophylaxis for 6 to 8 weeks provided better outcomes compared to no action but not necessarily to treatment only. Outcomes for no action and treatment only were subject to a greater spread of uncertainty than those with adequate prophylaxis. For the base-case scenario ($R_0=2.5$, Figure 3, main manuscript), 6 weeks of prophylaxis had a marginal advantage over treatment only, while 8 weeks or more had a clear advantage over treatment.

Other parameters pertaining to transmission dynamics

Tables A5 and A6 show that the transmission dynamics parameters affect both the intensity of transmission within the HCW population, as well as the timing of the HCW epidemic.

From a baseline of no patient-to-HCW transmission, even a small increment of patient-to-HCW transmission had the potential to increase peak absenteeism in HCWs (Table A5); the effect, however, saturated at higher values of H/P. With regards to epidemic timing, when patient-to-HCW transmission was minimized ($H/P = 0$), the HCW epidemic peaked at the same time as the peak in the general population. Increasing the H/P ratio shifted the HCW epidemic forward, such that it precedes that in the general population. At extreme values of H/P, the HCW epidemic peaked before the start of HCW prophylaxis. This occurred at about $H/P = 2.08$ for base case parameters. Therefore, for the subsequent analyses, we used values for H/P up to 2.

As shown in Table A6, changing the extent of transmission attributable to HCW-to-HCW contact had minimal effect on both the peak absenteeism and the timing of the HCW epidemic.

Figures A5 to A10 show the combined effect of varying both patient-to-HCW and HCW-to-HCW transmission parameters simultaneously in two-way sensitivity analyses. For all relevant combinations of patient-to-HCW and HCW-to-HCW transmission shown with $R_0=2.5$, 6 weeks of prophylaxis was sufficient to be at least marginally superior to treatment only, while 8 weeks of prophylaxis was clearly superior to the treatment only strategy. For pandemics of shorter durations (either in the entire population with higher R_0 ; or within the HCW population with an increased H/P ratio), shorter durations of prophylaxis are superior to treatment only – the reduction of peak absenteeism for 4 weeks of prophylaxis were as effective as 8 weeks prophylaxis. For pandemics of longer durations (lower R_0 or decreased H/P ratio), prophylaxis is inferior to treatment only. At R_0 of 1.5 and at lower H/P, even 8 weeks of prophylaxis is insufficient. However, for these longer duration pandemics, overall peak absenteeism is already low.

Latent and infectious periods

Figure 4 in the main manuscript shows the peak absenteeism with different treatment and prophylaxis strategies varying rates of growth (ζ), latent periods (α), and infectious durations (γ). The centre set of figures in A12 with $\alpha = 2$ and $\gamma = 4.1$ was with our base case parameters. At low growth rates, although situations of inadequate prophylaxis are more likely, peak absenteeism is low ($<10\%$) regardless of the

strategy chosen, and is relatively insensitive to the choice of prophylaxis duration. At higher growth rates where peak absenteeism is $>10\%$, 6 weeks of prophylaxis is equal or superior to treatment alone, and 8 weeks is always substantially superior.

Discussion

From Figure A1, optimal results for the treatment only strategy are possible even without stockpiling of treatment doses for 100% of HCWs for a few reasons. Firstly, a proportion of HCWs remain uninfected during the pandemic; this proportion is dependent on the R_0 , and decreases with increasing R_0 because of the larger number of secondary infections. In addition, 33% of infected HCWs would be asymptomatic (base-case assumptions), and will not require treatment. Finally, to achieve suppression of peak absenteeism, the treatment stockpile only needs to cover slightly past the epidemic's peak; further treatment during the tail end of the epidemic will not have any effect on the peak. For example, in a base case pandemic with $R_0=2.5$, stockpiling for about 40% of HCWs would be sufficient to achieve optimal results (Figure A1).

However, pandemic preparedness plans should guard against all possibilities of spread. This would include the possibility of a 2nd or 3rd wave, the absence of effective vaccines, and increased infection rates for high-risk sub-populations such as HCWs. We assumed that sufficient treatment doses are available as planned in current prophylaxis strategies, because prophylaxis is always over and above stocks available for treatment. This may necessitate having 100% treatment coverage for all HCWs.

From the results, it is apparent that prophylaxis must cover the pandemic's peak to achieve a reduction of peak absenteeism over the treatment only strategy. As pandemics with higher R_0 (≥ 4) are 8 weeks or less in duration, stockpiles of 8 weeks would cover the entire pandemic duration. Additional stockpiles in such situations will not accrue additional benefits but only increase costs. To protect HCWs in the worst-case scenarios such as pandemics with high R_0 , fast spread, and high peak absenteeism; prophylaxis strategies for 6 to 8 weeks will be effective. This shields HCWs from the majority of infections occurring in the general population, leaving them to provide critical healthcare services during the pandemic's peak.

Under all circumstances, redistributing prophylaxis to extend the prophylaxis duration beyond the pre-determined duration does not have a substantial effect on peak absenteeism (Tables A1 and A2). This is because the utilization of prophylaxis doses is more than 93% for the important scenarios as mentioned above. For the scenarios where utilization falls below 90%, the majority of infections have taken place before the end of the pre-determined prophylaxis duration. In these situations, the redistribution of prophylaxis doses does not have substantial impact on absenteeism because the pandemic's peak has passed.

Current pandemic plans call for the distribution and consumption of prophylaxis for the specified duration because clinical influenza infection cannot be easily determined given the presence of other influenza-like illnesses, even with laboratory tests which will require time to develop and distribute. The only savings in prophylactic doses may be from the very small number of HCW deaths during prophylaxis, and from the fact that for every HCW developing clinical illness while on prophylaxis, 5 doses will

be saved from the prophylaxis stockpile if we draw the entire treatment course from the separate treatment stockpile. The duration of prophylaxis for all HCWs was therefore used to represent the strategies, as per current pandemic preparedness protocols, as it presents the most conservative scenario where the stockpiles are maximally utilized (although we have shown that either method of utilization results in similar conclusions).

From the one-way sensitivity analyses in Figures A2 and A4, the input parameter of "reduction in medical leave with treatment" and the parameters pertaining to the effects of prophylaxis all had substantial impact on the outcome. This shows that the outcome of peak absenteeism was sensitive to the treatment and prophylaxis strategies being considered in this study.

As shown in Table A1 and A4, treatment only was always superior to no action and should always be considered in preparedness plans. However, insufficient durations of prophylaxis can be detrimental compared to treatment only, depending on the assumptions about transmission dynamics, disease severity, and antiviral efficacy. Low R_0 pandemics with long durations tend to render prophylaxis insufficient. However, in these pandemics, the slow pick-up in the epidemic curve and relatively low peak absenteeism may allow policy makers to choose the appropriate strategy based on initial surveillance data.

From Table A6, changing the proportion of transmission attributable to HCW-to-HCW spread had a minimal effect on both peak absenteeism and timing of the HCW epidemic. This is because disease transmission among HCWs is dependent on HCW-to-HCW spread as well as acquisition of disease from the general population. These two modes of spread are correlated (Appendix 1) – increasing one proportion decreases the other, possibly negating the effects of the changes. The additional increase in peak absenteeism resides on patient-to-HCW spread, which is in turn dependent on the amount of protection provided to HCWs. Infection control and personal protective equipment may thus be important aspects of HCW protection during a pandemic.

Figures A5 to A10 reinforce the fact that for pandemics of shorter durations, shorter durations of prophylaxis are effective because they are sufficient to cover most of the pandemic's duration. It is during these pandemics (shorter duration and high peak absenteeism) that the impact will be greatest and where prophylaxis strategies will be effective.

Finally, because there have been different estimates of latent and infectious periods, we determined whether our conclusions would have been affected had different latent and infectious periods been assumed while fixing the growth rates of the epidemics. We see that, even for a broad range of epidemic scenarios, even very extreme choices of values for the latent period and infectious period would have little impact on the conclusions (Figure 4 of the main manuscript).

Policy Implications

Policy makers must consider stockpiling sufficient anti-virals to treat clinically infected HCWs. In addition, policy makers should consider prophylaxis from a risk

management perspective. Severe pandemics increase the strain on HCWs due to the numbers of patients and hospitalizations, and the reduced response capacity of healthcare services. Policies should therefore consider protection against high impact pandemics of short duration, high morbidity and mortality, and high peak absenteeism. In these pandemics, prophylaxis durations of 6 to 8 weeks will be effective across a range of scenarios, and have been shown in studies to be safe (5). As the amount of prophylaxis available for critical workers is relatively small compared to strategies for the entire country – such an investment may be cost-beneficial since critical functions cannot be sacrificed. While we prepare for worst-case scenarios, the actual pandemic may be prolonged and of lower impact. Pandemics of lesser severity will probably place fewer requirements on essential services, and this study showed that such pandemics also result in lower absenteeism rates – treatment and prophylaxis is less critical to service continuity. For such pandemics, policy makers will have sufficient time to reconsider their options during the pandemic itself.

Policy makers must also consider additional preventive measures in addition to anti-viral drugs. Public health and infection control measures must be emphasized together with anti-viral use, and not superseded by treatment or prophylaxis strategies.

Finally, surveillance networks are important to ensure that the appropriate strategy is adopted based on the projected epidemic curve during the early pandemic phases. Policy makers must be informed that untimely prophylaxis is detrimental to the outcome. Prophylaxis initiation should be held back until a certain point in the epidemic curve where prophylaxis has substantial impact and covers the pandemic's peak, although this may be difficult given public sentiment and pressure. Premature initiation may render prophylaxis less or ineffective. Information acquired from surveillance should influence policy decision appropriately, and further studies are needed to determine the ideal time for prophylaxis initiation and the role of surveillance in evaluating the pandemic phases and projected spread. If prophylaxis initiation is premature, treatment only may be the better option to reduce absenteeism.

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Table A1. Peak absenteeism by reproductive number and anti-viral strategy, with and without redistribution of prophylaxis doses

Repro- ductive number, R_0	Pandemic duration in weeks	Peak % absent by strategy without redistribution (peak % with redistribution, where applicable)								
		No action	Treat- ment only	Planned duration of prophylaxis, in weeks						
				2	4	6	8	10	12	14
1.5	24	2.8	2.1	2.1 (2.1)	2.1 (2.1)	2.2 (2.2)	2.3 (2.3)	2.4 (2.4)	2.1 (2.1)	1.4 (1.4)
2	15	6.7	5.1	5.2 (5.2)	5.5 (5.5)	5.9 (5.9)	4.6 (4.5)	1.8 (1.5)	1.1 (1.1)	1.1 (1.1)
2.5	12	10.2	7.9	8.1 (8.1)	8.8 (8.8)	7.2 (7.0)	2.0 (1.8)	1.8 (1.8)	1.8 (1.8)	1.8 (1.8)
3	10	13	10.2	10.6 (10.6)	11.4 (11.4)	4.7 (3.9)	2.5 (2.5)	2.5 (2.5)	2.5 (2.5)	2.5 (2.5)
4	8	17.3	13.9	14.6 (14.6)	10.8 (10.1)	3.7 (3.7)	3.7 (3.7)	3.7 (3.7)	3.7 (3.7)	3.7 (3.7)
6	6	22.5	18.5	19.7 (19.7)	5.5 (5.5)	5.5 (5.5)	5.5 (5.5)	5.5 (5.5)	5.5 (5.5)	5.5 (5.5)
Pandemic similar to 1918 “Spanish Flu”*		20.2	15.1	15.8 (15.8)	11.6 (11.0)	4.1 (4.1)	4.1 (4.1)	4.1 (4.1)	4.1 (4.1)	4.1 (4.1)

* $R_0 = 4$, mortality = 5%, (hospitalization set to the ratio of the hospitalization rates to the case fatality rates in Table 1)

Table A2. Prophylaxis doses utilized at the end of the pre-determined prophylaxis period, under the assumption that prophylaxis can be redistributed.

Repro- ductive number (R_0)	Number of prophylaxis doses used at the end of the pre-determined prophylaxis period (% of total prophylaxis stockpile), by weeks of prophylaxis						
	2 weeks	4 weeks	6 weeks	8 weeks	10 weeks	12 weeks	14 weeks
1.5	279,722 (99.9%)	559,834 (100%)	839,146 (99.9%)	1,117,660 (99.8%)	1394290 (99.6%)	1666850 (99.2%)	1935180 (98.7%)
2	279,823 (99.9%)	559,817 (100%)	837,308 (99.7%)	1,106,720 (98.8%)	1363390 (97.4%)	1612570 (96%)	1860210 (94.9%)
2.5	279,843 (99.9%)	559,258 (99.9%)	829,496 (98.7%)	1,079,280 (96.4%)	1319340 (94.2%)	1557250 (92.7%)	1795360 (91.6%)
3	279,837 (99.9%)	557,752 (99.6%)	814,639 (97%)	1,050,350 (93.8%)	1282130 (91.6%)	1513100 (90.1%)	1744450 (89%)
4	279,769 (99.9%)	549,723 (98.2%)	782,356 (93.1%)	1,005,170 (89.7%)	1252010 (89.4%)	1477770 (88%)	1703940 (86.9%)
6	279,262 (99.7%)	524,068 (93.6%)	738,258 (87.9%)	950,818 (84.9%)	1227310 (87.7%)	1449020 (86.3%)	1671110 (85.3%)

Table A3. Treatment and prophylaxis doses required for the base case scenario under the assumption that prophylaxis is consumed by all HCWs for the pre-planned duration. Equivalent treatment doses for the general population are shown.

Strategy	Treatment doses	Prophylaxis doses	*Equivalent treatment doses for the general population (%)
Treatment only	121,158	0	0.28
Prophylaxis 2 weeks	120,889	280,000	0.92
4 weeks	117,337	560,000	1.56
6 weeks	91,330	840,000	2.14
8 weeks	52,098	1,120,000	2.69
10 weeks	35,383	1,400,000	3.30
12 weeks	32,034	1,680,000	3.94
14 weeks	31,559	1,960,000	4.58

* includes sum of treatment and prophylaxis doses used for HCWs

Table A4: Multi-way sensitivity analysis for peak HCW absenteeism under different strategies and values of R_0

Repro- ductive number, R_0	Peak absenteeism, Median % (5 th , 95 th percentile)					
	No action	Treatment only	Planned duration of prophylaxis, in weeks			Prophylaxis throughout*
			4	6	8	
1.5	2.8	2.1	2.2	2.2	2.3	0.3
	(1.9,3.6)	(1.1,3)	(1.1,3.1)	(1.1,3.1)	(1.2,3.3)	(0.1,0.6)
2	6.7	5.1	5.6	6.0	4.6	0.9
	(4.5,8.6)	(2.7,7.3)	(2.8,7.8)	(3.2,8.3)	(2.5,6.6)	(0.4,1.6)
2.5	10.3	8.0	9.0	7.3	2.1	1.6
	(7,12.8)	(4.4,11.1)	(4.8,12.0)	(4.0,9.9)	(1.1,3.1)	(0.7,2.6)
3	13.2	10.3	11.5	4.7	2.2	2.2
	(8.8,16.4)	(5.2,14)	(6.6,15.5)	(2.6,6.7)	(0.9,3.6)	(0.9,3.6)
4	17.4	13.9	10.9	3.3	3.3	3.3
	(12.3,21.5)	(7.6,18.7)	(6.3,14.5)	(1.5,5.4)	(1.3,5.3)	(1.3,5.3)
6	22.5	18.8	5.0	4.9	4.9	4.9
	(16.3,27.6)	(10.8,24.3)	(2.5,7.8)	(2.1,7.9)	(2.0,8.0)	(2.1,7.9)

*Assumes prophylaxis is sufficient to cover entire pandemic duration

Table A5: Effect of changing R_0 and patient-to-HCW transmission (H/P ratio) on peak absenteeism and timing of peak absenteeism

R_0	1.5		2.0		2.5	
Patient-to-HCW transmission (H/P ratio)	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*
0	2.8	190.1	6.7	110.3	10.2	81.2
0.01	4.3	177.9	8.6	102.7	12.1	75.7
0.1	5.7	154.4	10.4	88.5	14.0	65.9
1	6.0	124.5	10.8	72.9	14.3	54.3
10	6.1	93.7	10.8	56.3	14.4	42.5
Timing of peak prevalence, general population*	190.1		110.3		81.2	
R_0	3.0		4.0		6.0	
Patient-to-HCW transmission (H/P ratio)	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*
0	13.0	65.8	17.3	49.5	22.5	35.3
0.01	14.8	61.4	18.8	46.4	23.4	33.3
0.1	16.7	53.6	20.6	40.6	25.0	29.3
1	17.1	44.4	21.0	34.0	25.4	24.7
10	17.2	35.1	21.1	27.2	25.5	20.2
Timing of peak prevalence, general population*	65.8		49.5		35.3	

*Time in days from introduction of first infectious case

Table A6: Effect of changing R_0 and HCW-to-HCW transmission (ω) on peak absenteeism and timing of peak absenteeism

R_0	1.5		2.0		2.5	
HCW-to-HCW transmission (ω)	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*
0.2	2.8	190.0	6.7	110.2	10.2	81.2
0.5	2.8	190.0	6.7	110.2	10.2	81.2
0.8	2.8	190.0	6.7	110.3	10.2	81.3
Timing of peak prevalence, general population*	190.1		110.3		81.2	
R_0	3.0		4.0		6.0	
HCW-to-HCW transmission (ω)	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*	Peak absenteeism without treatment, HCWs (%)	Timing of peak absenteeism, HCWs*
0.2	13.0	65.8	17.3	49.5	22.5	35.3
0.5	13.0	65.8	17.3	49.5	22.5	35.3
0.8	13.1	65.9	17.4	49.6	22.6	35.4
Timing of peak prevalence, general population*	65.8		49.5		35.3	

*Time in days from introduction of first infectious case

Figure A1. Peak absenteeism for different treatment stockpile sizes, under different R_0

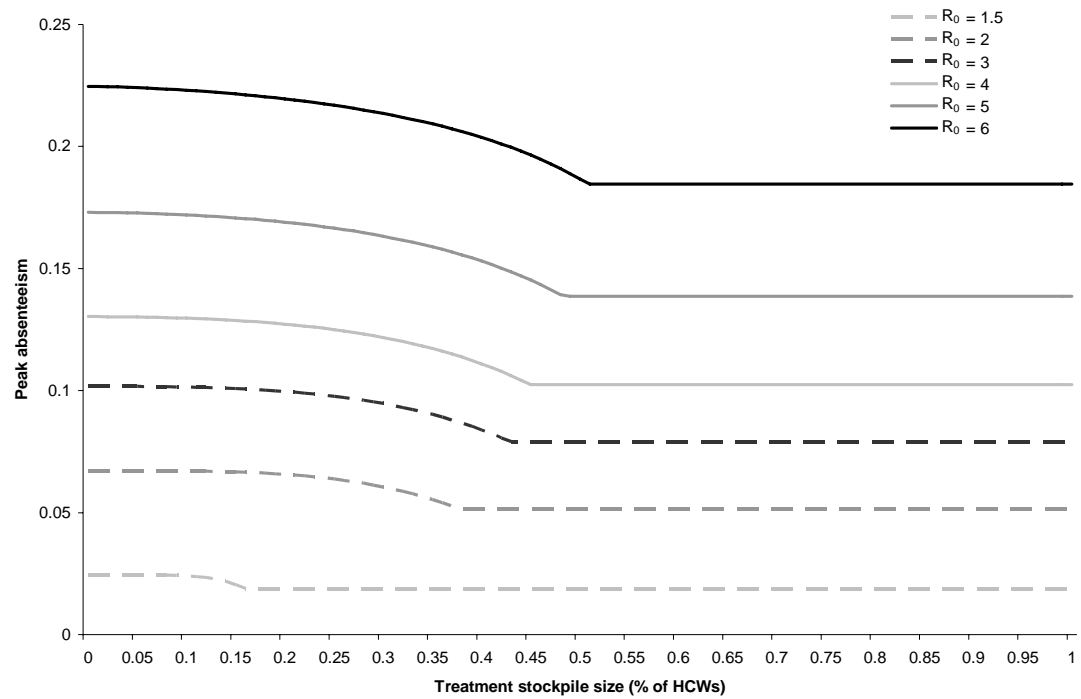


Figure A2. One-way sensitivity analysis for the strategy of no action, by R_0 .

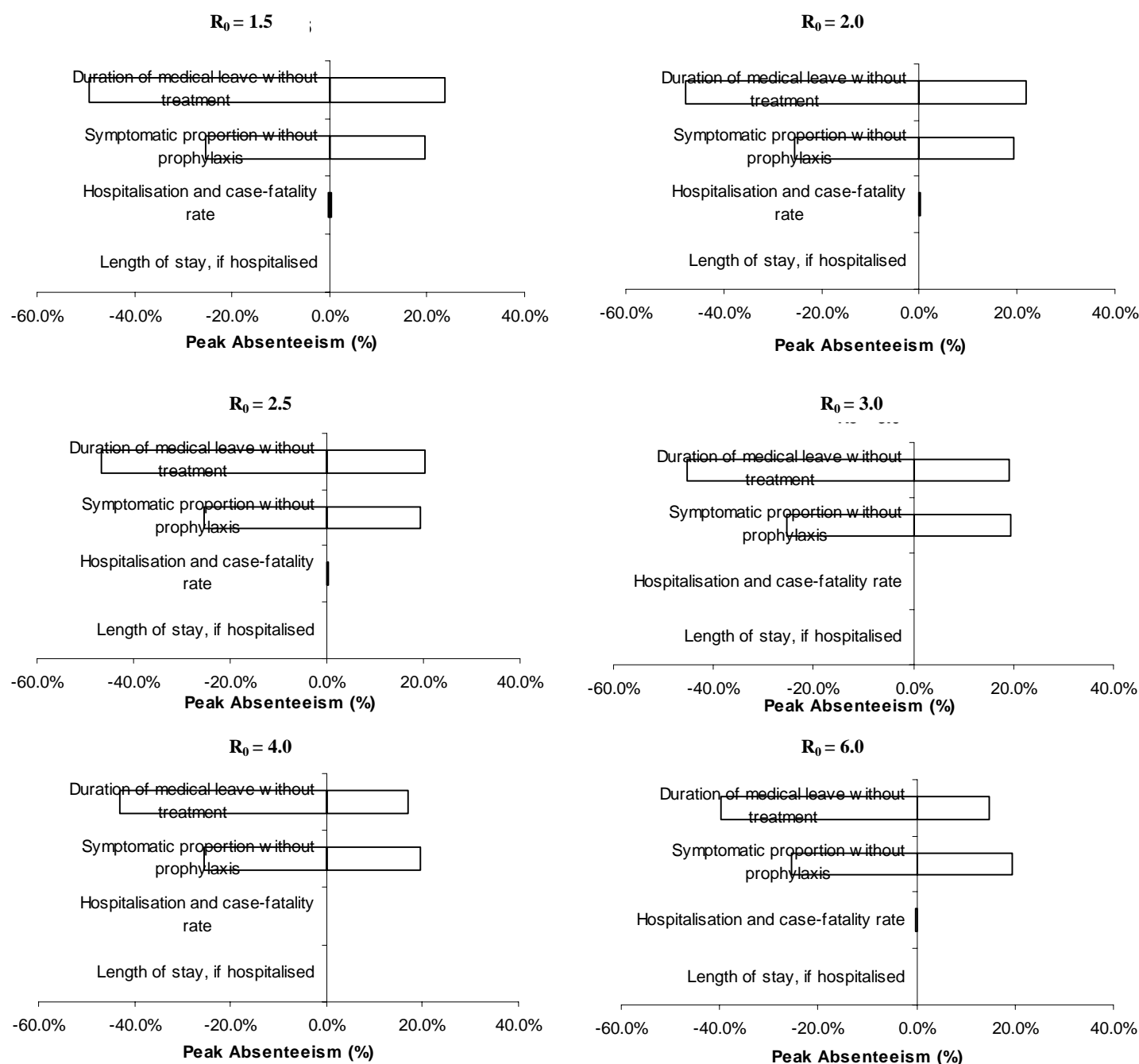


Figure A3. One-way sensitivity analysis for the strategy of treatment only, by R_0 .

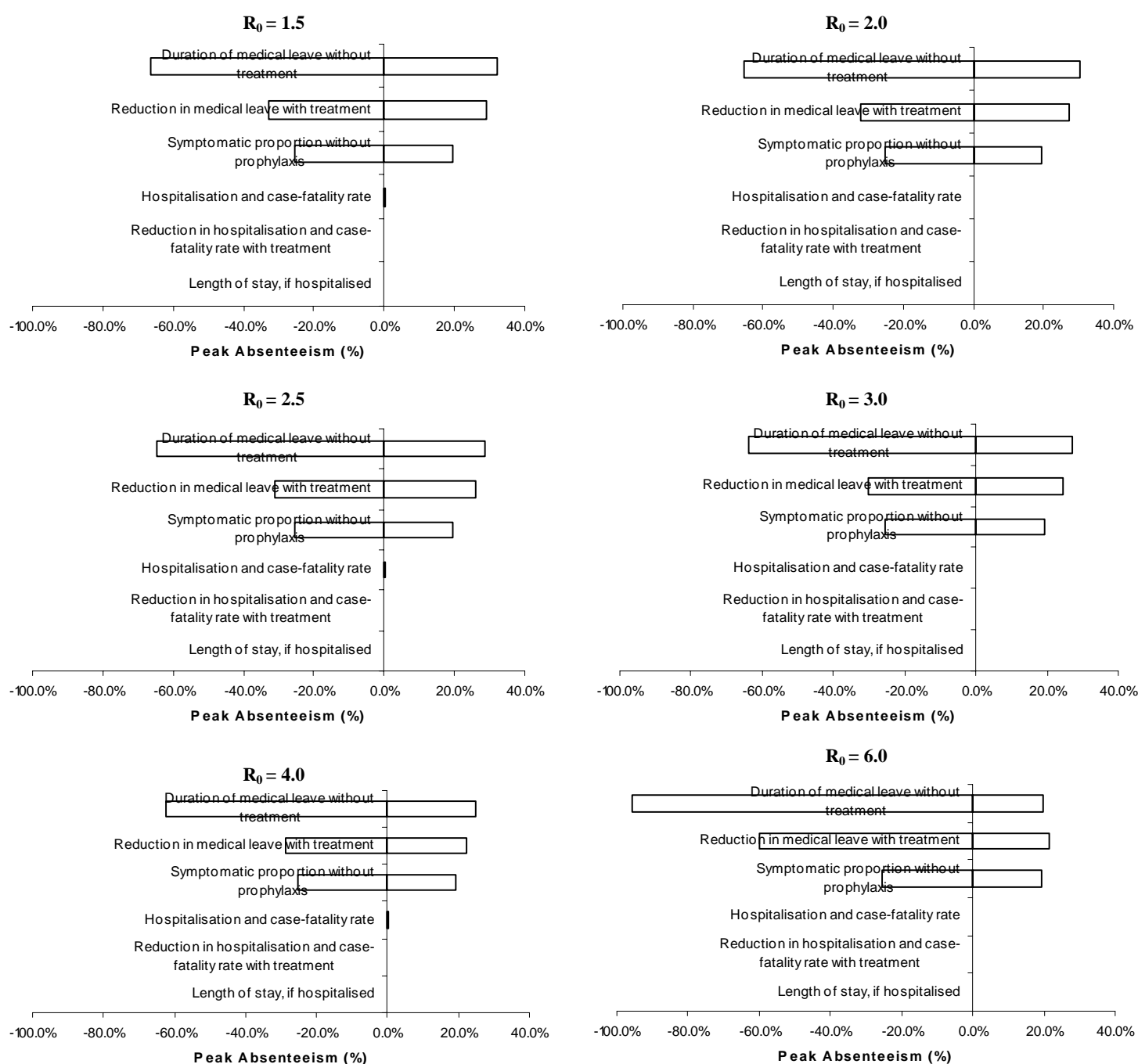


Figure A4. One-way sensitivity analysis for the strategy of prophylaxis, by R_0 .

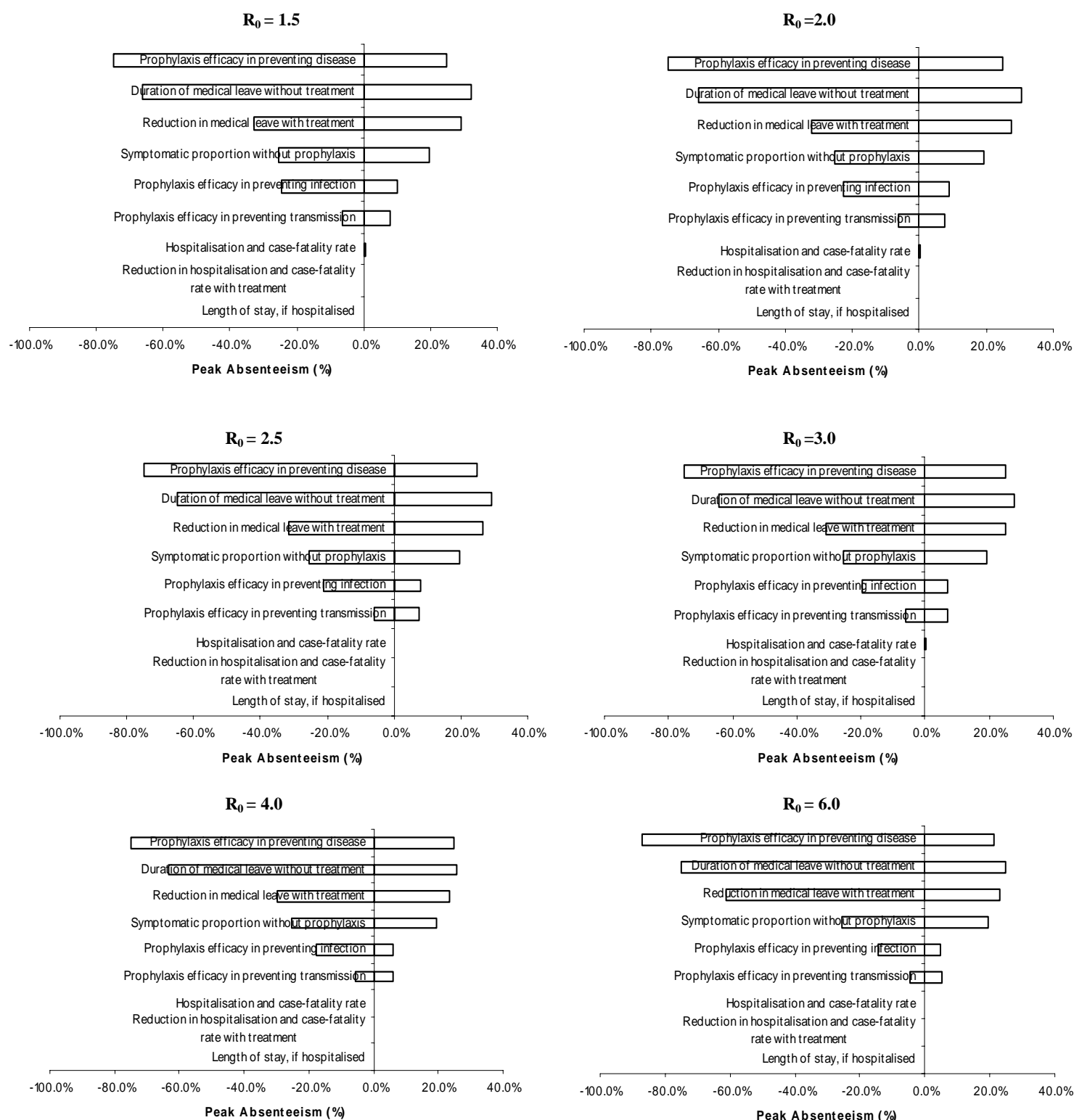


Figure A5. Peak absenteeism by treatment and prophylaxis strategies, H/P ratios, and HCW-to-HCW transmission (ω), for $R_0=1.5$. (Tx refers to treatment, Rx refers to prophylaxis)

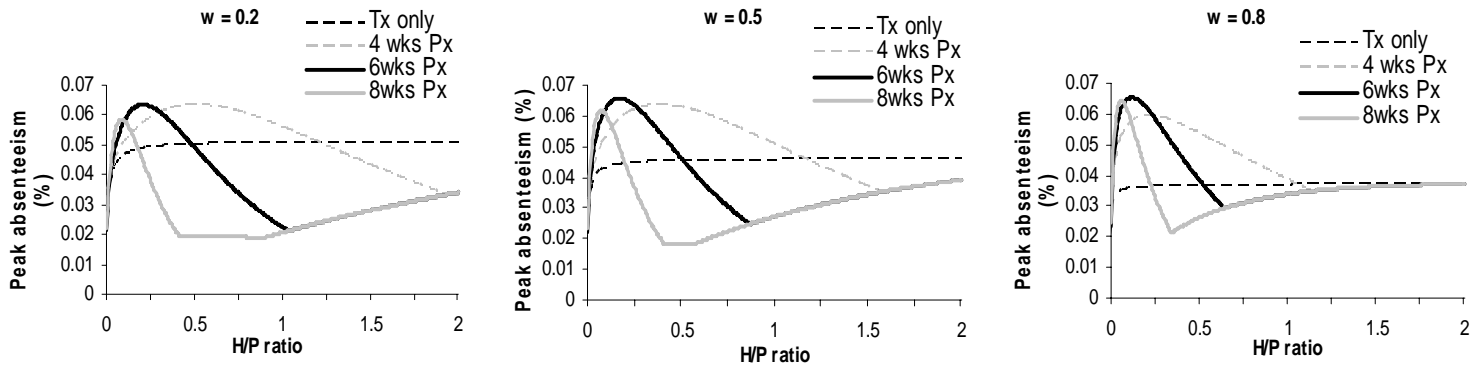


Figure A6. Peak absenteeism by treatment and prophylaxis strategies, H/P ratios, and HCW-to-HCW transmission (ω), for $R_0=2.0$. (Tx refers to treatment, Rx refers to prophylaxis)

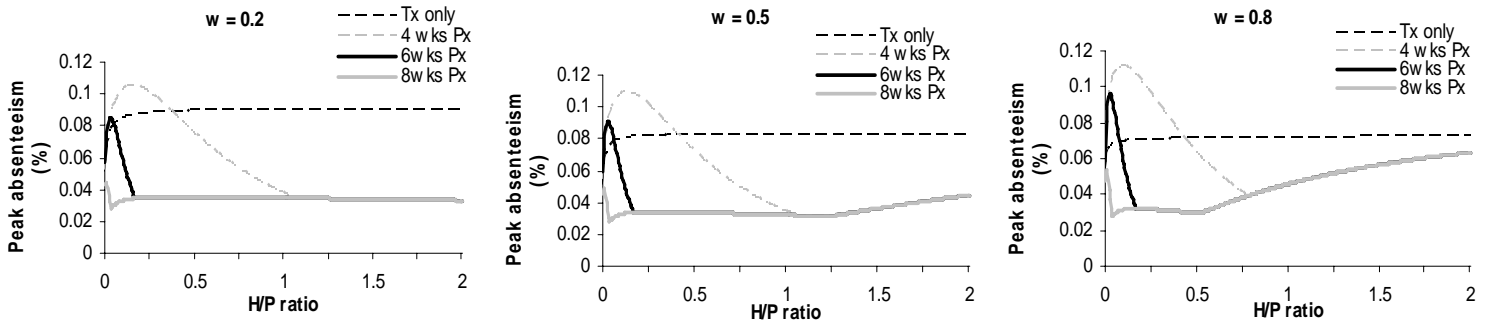


Figure A7. Peak absenteeism by treatment and prophylaxis strategies, H/P ratios, and HCW-to-HCW transmission (ω), for $R_0=2.5$. (Tx refers to treatment, Rx refers to prophylaxis)

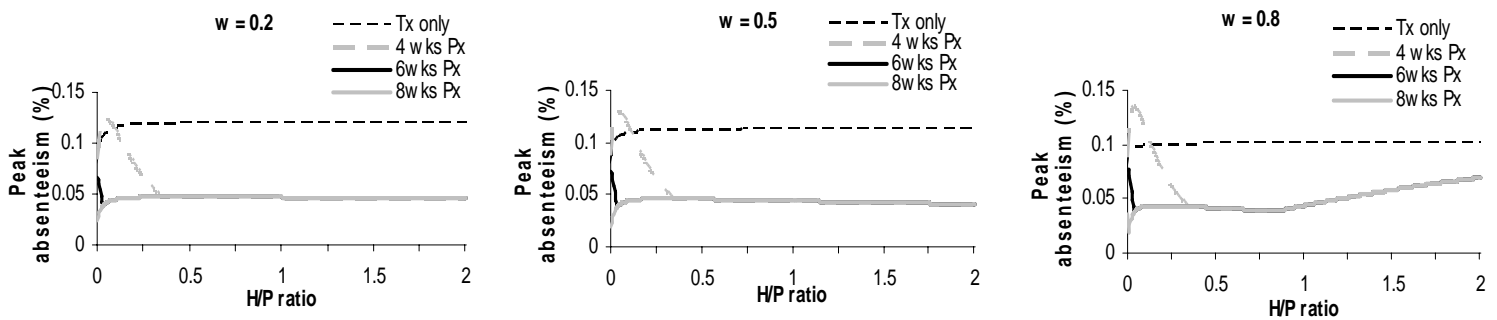


Figure A8. Peak absenteeism by treatment and prophylaxis strategies, H/P ratios, and HCW-to-HCW transmission (ω), for $R_0=3.0$. (Tx refers to treatment, Rx refers to prphylaxis)

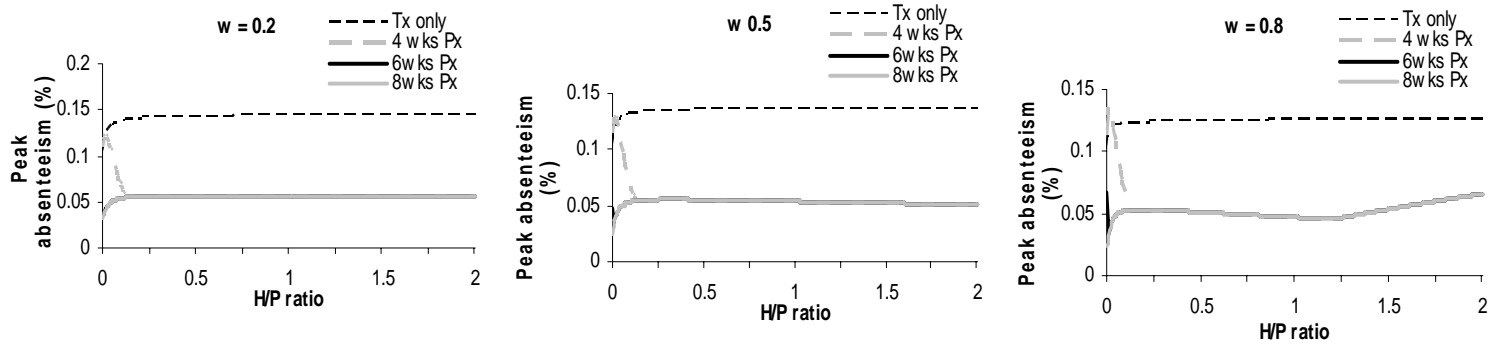


Figure A9. Peak absenteeism by treatment and prophylaxis strategies, H/P ratios, and HCW-to-HCW transmission (ω), for $R_0=4.0$. (Tx refers to treatment, Rx refers to prphylaxis)

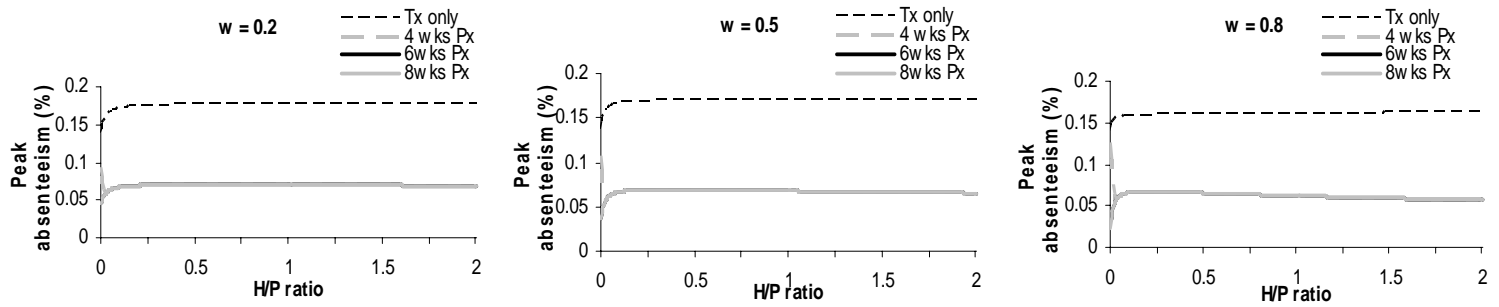


Figure A10. Peak absenteeism by treatment and prophylaxis strategies, H/P ratios, and HCW-to-HCW transmission (ω), for $R_0=6.0$. (Tx refers to treatment, Rx refers to prphylaxis)

